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| 08/653,294 | 05/24/96 | CLAYBERGER C | 286002020023 |

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| EXAMINER | |
|---|---|
| CUNNINGHAM, T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED:
05/26/98

**Please find below a communication from the EXAMINER in charge of this application.**

Commissioner of Patents

| Office Action Summary | Application No. 08/653,294 | Applicant(s) Clayberger et al. |
|---|---|---|
| | Examiner Thomas Cunningham | Group Art Unit 1644 |

☒ Responsive to communication(s) filed on *Mar 10, 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-26* is/are pending in the application.

Of the above, claim(s) *22-26* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

1. Claims 1-21 are active. This action is responsive to Paper No's 12 and 14-16.

2. The amendment of page 4, line 26 changing the term "N-terminal" to "C-terminal" is not objected to in view of the Applicant's explanation on pages 3-4 of the last response. Further basis for this correction is present on pages 3 and 9 of the specification as originally filed.

The amendment to page 34, line 25 is not objected to as it is clear from the context of the specification as filed that this change merely corrects a typographical error.

The Examiner appreciates the Applicant clearly pointing out support in the specification as filed for the changes made in the recent amendemnt.

3. (Withdrawn) The prior objection to the oath/declaration is withdrawn in view of the Applicant's comments on page 6 of the last response. If the priority claim is amended in the future this would most likely be considered a new issue necessitating further search or consideration and the finality of this or a subsequent office action may be maintained on this basis.

4. The prior rejections under 35 U.S.C. 112, second paragraph are withdrawn or maintained as follows:

A. (Withdrawn) The prior rejection of claim 18 as being vague and indefinite as to the metes and bounds of "MHC unmatched donor" is withdrawn in view of the amended claim language which now recites "allogeneic or xenogeneic MHC donor".

B. (Withdrawn) The prior rejection of claim 18 as being indefinite as to the characteristics of a "predetermined regimen" is withdrawn in view of the amended claim language and in view of Applicant's comments on page 7 of the last response.

C. (Withdrawn) The prior rejection of claims 18-20 as being indefinite in the use of the terms "extend the period of acceptance" or "inhibit transplant rejection" is withdrawn in view of the Applicant's comments on page 8 of the last response.

D. (Withdrawn) The prior rejection of claim 19 as being vague in the use of the phrase "subtherapeutic dosage" is withdrawn in view of the Applicant's clarification on pages 8-9 of the last response.

E. (Withdrawn) The prior rejection of claims like 19-20 as being unclear as to the metes and bounds of the term

"immunosuppressant" is withdrawn in view of the Applicant's broad, functional definition (e.g. compounds which generally debilitate the immune system) of this term as described by the comments on pages 9-10 of the last response. The Applicant has also pointed out specific exemplification of immunosuppressants in the instant specification, see page 15, lines 8-17.

F. (Moot) The prior rejection of claims like 1 and 21 as being unclear as to the metes and bounds of the term "peptide-type" compound is moot in view of the cancellation of this term from the claim language.

G. (Withdrawn) The prior rejection of claim 1 for being unclear as to which amino acids are "hydrophobic or small" amino acids is withdrawn in view of Applicant's comments on pages 10-11 of the last response.

H. (Withdrawn) The prior rejection of claim 1 as being unclear as to the metes and bounds of the term "immunomodulating" is withdrawn in view of the amended claim language and Applicant's explanation on page 11 of the last response. This term is now limited to modulation of lymphocyte activity, usually determined by assays such as those measuring CTL-mediated lysis or proliferation.

I. (Maintained) It is unclear whether the language of claim 1 is open or closed. Is the recited compound limited to peptides 60 amino acids or less? The language has been interpreted as being open. A compound which comprises 60 residues has no upper defined length limit, so long as it comprises at least 60 residues. Clarification is required.

4. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for particular peptides such as the sequences demonstrated to inhibit cytolysis on pages 21-et seq. of the specification, does not reasonably provide enablement for all the peptides encompassed by broad claim language.

A. (Withdrawn) In vivo usage not enabled. One with skill in the art would not reasonably expect to be able to use the claimed compounds, peptide compounds and peptide conjugates because it would be unpredictable and require undue experimentation to determine whether such peptide-based products would exert functionally useful effects on CTL responses in vivo. Peptide compounds that comprise allogeneic (non-self) alpha-1 domain sequences would be expected to be recognized as foreign by a subject and eliminated. Further, short peptides, in general, when administered in vivo would be expected to be degraded or metabolized by host mechanisms, such as by serum proteases, or hepatic or immunological clearance mechanisms prior to exerting useful effects of a subject's CTL's. Additionally, one would expect that effective concentrations of the claimed peptide products could not be achieved in vivo, due to the aforementioned clearance mechanisms, or the presence of anatomical barriers limiting their access to a subject's CTL's.

B. (Withdrawn) Xenotransplantation. The specification does not provide a reasonable expectation that the claimed methods could be used to extend the period of acceptance for xenogeneic transplants. There is no claim language limiting the claimed methods to transplants within a particular species, e.g. allogeneic transplants. Due to the genetic differences between MHC, T cell receptor, and accessory molecule determinants of different species, one with skill in the art would not expect that MHC protein sequences from one species (e.g. the HLA molecules of humans) would be capable of blocking immune responses in another species. Although there is description of xenogeneic organ transplants on page 22, line 18 of the specification, one with skill in the art would not have a reasonable expectation that the claimed peptides would prolong the survival of such xenogeneic transplants for the reasons set forth above.

C. (Withdrawn) Allotransplantation/MHC Restriction. The methods have not been limited to inhibition of CTL's which have shared MHC specificity with the administered peptide. According to page 26 of the specification of the parent application 08/222,851 "The results in Table 2 indicate that only whether the CTL's and the target cells share A2 specificity to the A2-derived peptides provide inhibition". E.g. the administered peptide would have to be matched to the HLA type of the transplanted organ, and would be expected only to inhibit that portion of host CTL response directed to that particular HLA molecule.

Thus, where a transplanted organ has multiple HLA, other antigen mismatches with a host, administration of a single peptide would be expected to at best reduce immune response to a single HLA antigen. Whether, reduction of only a portion of the CTL response would result in a prolongation of graft survival by reducing rejection phenomena below a particular threshold would be unpredictable.

D. (Withdrawn) Regimen. The ability of the claimed methods to prevent rejection depends on the particular steps in the regimen, see e.g. page 14 of the specification. The claims have not been limited to regimes that would be expected to reduce rejection of allo- or xenografts. E.g. oral or inhalational administration of the peptides would not be expected to put them in contact with CTLs mediating graft rejection. Whether the peptide is administered prior to allografting or after would also be expected to be critical to the type of suppressive effect

achieved, see e.g. page 31, lines 17-19 of the specification which indicate that timing of the dosages is critical.

E. (Maintained) Diverse peptides. Claims 1-12 reads broadly on use of peptides comprising residues 75-84 of any HLA-B alpha chain. However, page 40, lines 1-5 indicate that only peptides having sequences corresponding to particular alleles of HLA-B alpha 1 block CTL responses. E.g. HLA-B2702 blocks, but HLAB2705 does not. It would be unpredictable which peptide species would be capable of multiallele blocking without testing of different peptide species on a case-by-case basis. For instance, pages 21-22 of the specification disclose that the HLA-B2702.75-84 and HLA-B2705.75-84 peptides, though differing in only three residues have materially different effects: the HLA-B2702 peptide inhibited lysis; the HLA-B2705 peptide did not.

--See arguments at end of section.

F. (maintained) Variants. Claims 1-21 also encompass variants of the recited (HLA-B derived) peptide sequences. It would be unpredictable which mutations of an HLA-B 75-84 sequence would retain the critical functional property of being able to inhibit CTL activity because such mutations would be expected to affect functional binding of the peptide to the T cell receptor or accessory molecules. Modifications to the recited peptides,

whether the addition, substitution, or deletion of amino acid residues, or the joining of such peptides to other chemical moieties would be expected to have unexpected, unpredictable effects on the activity of the particular peptide to modulate CTL responses, see e.g. Bowie, et al., Science 247:1306-1310 (1990). It is unclear how the peptides are actually modulating CTL responses, but one with skill in the art would expect that the claimed peptide compounds are interfering with the T cell receptor (TCR) antigen presenting cell interaction. It is unclear on a structural basis which types of modifications can be made to a "blocking" or stimulatory peptide and still have it exert its functional effect. For instance a stimulatory peptide that had bulky, sterically hindering chemical moieties joined to it would not be expected to effectively stimulate CTL responses, because the additional moieties would be expected to prevent it from binding to the sites on the CTL or the APC necessary for inducing CTL stimulation. Each chemical modification of a peptide known to modulate CTL activity would have to be investigated on a case-by-case basis and thus would impose a burden of undue experimentation on one with skill in the art.

--See arguments at end of section.

G. (Withdrawn) Subtherapeutic dosage. The specification does

not adequately describe the parameters of the term "subtherapeutic dosage", as used e.g. in claims 19 and 20. Does an immunosuppressant in a subtherapeutic dosage have no effect on transplant survival time? How would one with skill in the art determine what was or was not a subtherapeutic dosage of a particular immunosuppressant?

H. (Maintained) Immunosuppressive agent required. According to page 31 of the specification allograft survival was similar in control and peptide-treated groups. Only groups treated with CsA had significant increases in graft survival time.

--Applicant's arguments on page 18 of the response have been considered. However, claims like claim 18 have not limited to provision of the recited peptides along with an immunosuppressant. Evidence that the recited peptides alone would have activity in increasing allograft survival would be helpful.

I. (Withdrawn) The recited immunomodulating activity, see e.g. claim 1, appears to be limited to reductions in CTL cytotoxicity or proliferation. The specification does not describe that other types of immunological mechanisms are affected by treatment with the recited peptides. See e.g. the lack of activity of the recited peptides on antibody responses as mentioned in section G of page 34 of the specification.

--This issue is withdrawn in view of the limitation to inhibition of "lymphocyte activity".

J. (Maintained) The compound of claim 1 appears to be a peptide homo- or heterodimer. One would expect that only certain types

of dimeric compounds have the ability to reduce CTL responses because different configurations of dimers would have different structures or spacing of determinants, and therefore different functional abilities to compete or bind to T cell ligands or MHC Class I molecules. Since a particular mechanism of action for the peptide dimers has not been adequately described, it would be unpredictable which structures would retain functional activity.

--See below.

--Applicant urges that the scope of the instant claim language is supported by at least 17 separate examples of peptides and refers to Table 1 at page 21 of the specification. However, Table 1 only exemplifies dimers of the "beta-alpha variety" i.e. those comprising the (a84-79)-(aa79-84) conjugate, but it does not exemplify alpha-alpha, beta-beta or alpha-beta dimers. Different tertiary or quaternary configurations would be expected to have unpredictable effects on function. For instance, the top of page 22 of the specification indicates the unpredictability of structural variation on lytic ability, because length as well as presence of an inverted repeat dimer had different effects on cytolysis.

Further, only dimers derived from residues 75-84 of a particular HLA allelic product, HLA-B2702, are exemplified. One with skill in the art would recognize that different MHC alleles encode product with different amino acid sequences and that variation in an amino acid sequence would have unpredictable effects on functional activity. A case in point: page 22, lines

19-20 indicate that dimers formed from residues of the B7 allelic product did not inhibit CTL-mediated lysis at any concentration tested.

Applicant urges that only a limited number of peptides must be tested, and that such testing only requires routine experimentation. However, the instant claim language reads on thousands of different peptide analogs of which the Applicant has exemplified only a few as retaining an enhanced ability to modulate CTL activity. For instance for homodimers of a particular sequence consisting of only residues 79-84, there would be (2)(2)(6)(2)(2)(6)= 576 different possible analogs. However, once optional residues are figured in, as well as permutations of different heterodimers and palindromic dimers, the numbers of analogs become very great. Most of these analogs would not be expected to be functional based on the species exemplified in the specification and evidence of record. Limitation of the claims to sequences spanning residues 75-84 and occurring naturally in MHC Class I proteins, and a demonstration that a significant number of such sequences retain an ability to modulate CTL activity would be helpful in addressing this rejection.

The declaration of Dr. Clayberger, Paper No. 16, has been considered, but is directed to less polymorphic segments of MHC Class I molecules comprising residues 75-84. It is noted that

the instant claims are directed to segments spanning residues 79-84, optionally containing residues 75-78. Thus, the declaratory evidence as well as the exemplified species in the specification, do not fully support the scope of the invention as claimed.

8. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson, U.S. patent 5,073,540 or WO88/05784 (published 11 August 1988). Olsson disclose peptides useful as antagonists or agonists for membrane receptors. The prior art compounds have essentially the same structure as those of the instant application, see e.g. cols. 7 and 8. WO88/05784 discloses similar peptides, see e.g. claim 1. WO88/05784 also suggests modification of such peptides using conventional techniques to extent their biological halflives, see pages 21-23. Page 10 of the specification describes such conventional techniques.

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the prior art peptides and to test functional activity on surface receptors or lymphocyte activity of the modified peptides using the assays disclosed in Olsson col.s 12-14 or by WO88/05784 on page 25. Further, page 40 of WO88/05784 explicitly suggests use of such peptides for prolonging graft survival time by reducing rejection cytolytic CTL activity.

Claims limited to products reasonably expected to retain the unexpected properties attributed to dimeric products, such as the dimer described in Table 1, would be free of this rejection. Applicant is encouraged to contact the Examiner telephonically to discuss this issue.

--Applicant urges that there is no motivation in the prior art to produce dimers. However, one with ordinary skill in the art would at least expect that dimers of the same unit would exert the same functional effects as a monomer. It is noted that the claim language is not limited to palindromic dimers--e.g. (aa79-84)-(aa84-79). Claim 1 encompasses α-β dimers that "may be the same or different". Thus, dimers such as (aa79-84)-(aa79-84) are NOT excluded from the language of claim 1. The prior art rejection is maintained for such dimers. For palindromic dimers this rejection would be dropped.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is

not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D, J.D. whose telephone number is (703) 308-3968. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800